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What happens after menopause? (WHAM): A prospective controlled study of vasomotor symptoms and menopause-related quality of life 12 months after premenopausal risk-reducing salpingo-oophorectomy

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HIGHLIGHTS

- Vasomotor symptoms increase by 3 months following premenopausal RRSO and persist but do not worsen by 12 months.
- Almost all women report these vasomotor symptoms as "mild".
- Hormone therapy reduces but does not resolve vasomotor symptoms after RRSO.
- Hormone therapy improves menopause related quality of life but not to pre-RRSO levels.

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ABSTRACT

Objective. To measure menopausal symptoms and quality of life up to 12 months after risk-reducing salpingo-oophorectomy (RRSO) and to measure the effects of hormone therapy.

Methods. Prospective observational study of 95 premenopausal women planning RRSO and a comparison group of 99 who retained their ovaries. Vasomotor symptoms and menopausal-related quality of life (QoL) were measured by the Menopause-Specific QoL Intervention scale at baseline, 3, 6 and 12 months. Chi-square tests measured differences in prevalence of vasomotor symptoms between RRSO vs the comparison group and by hormone therapy use. Change in QoL were examined with multilevel modelling.

Results. Three months after RRSO hot flush prevalence increased from 5.3% to 56.2% and night sweats from 20.2% to 47.2%. Symptoms did not worsen between 3 and 12 months and remained unchanged in the comparison group ($p<0.001$). After RRSO, 60% commenced hormone therapy. However, 40% of hormone therapy uses continued to experience vasomotor symptoms. After RRSO, 80% of non-hormone therapy users reported vasomotor symptoms. Regardless of hormone therapy use, 86% categorized their vasomotor symptoms as "mild" after RRSO. Following RRSO, Menopause-related QoL deteriorated but was stable in the comparison group (adjusted coefficient = 0.75, 95%CI = 0.55-0.95). After RRSO, QoL was better in hormone therapy users vs non-users (adjusted coefficient = 0.49, 95%CI = 0.20-0.78).

Conclusions. Vasomotor symptoms increase by 3 months after RRSO but do not worsen over the next 12 months. Hormone Therapy reduces but does not resolve vasomotor symptoms and may improve QoL, but not to pre-oophorectomy levels.

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1. Introduction

Ovarian cancer is the fifth most common female cancer with survival rates below 50% at 5 years [1]. Carriers of pathogenic variants in genes that increase hereditary risk for ovarian cancer, such *as brca1 and brca2* have an elevated risk of ovarian cancer of up to 44% [2,3]. With increasing access to rapid, low-cost gene sequencing, more women are identified with these pathogenic variants and only risk-reducing salpingo-oophorectomy (RRSO) reduces ovarian cancer and all-cause mortality in this population [4,5]. The National Comprehensive Cancer Network recommends RRSO at age 35–40 years in women with BRCA1 and 40–45 for those with BRCA2 mutations [6].

Few prospective studies have measured vasomotor symptoms (VMS) or other aspects of menopause-related quality of life (QoL) after premenopausal RRSO. Cross-sectional and retrospective studies consistently report that premenopausal oophorectomy leads to more sudden, severe and/or persistent VMS compared to natural menopause [7,8]. However the prospective impact on menopause-related QoL is uncertain [9,10].

Hormone therapy (HT) is the most effective treatment for VMS and may improve menopause-related QoL in postmenopausal women [11]. Whilst HT is recommended after RRSO for those without contraindications, uptake is suboptimal [12]. The efficacy of HT for VMS and quality of life after RRSO is uncertain [9]. For high-risk women, concerns about managing menopausal symptoms after RRSO are a barrier to potentially life-saving surgery [13].

The aim of this study was to measure the prevalence, trajectories and severity (as measured by bother) of vasomotor and other menopausal symptoms following RRSO to inform clinical decision making and patient care. This study focused on the first 12 months after RRSO and recruited a comparison group of same-aged premenopausal women who retained their ovaries and were predominantly at population risk of ovarian cancer. There were three specific aims: (1) to measure the prevalence and degree of bother from VMS, (2) to investigate changes in menopause-related QoL and (3) to compare the prevalence and bother of VMS and menopause related QoL between HT users and non-HT users.

2. Methods

2.1. Study design and population

This was a multicenter prospective observational study. The RRSO group were premenopausal women at high risk of ovarian cancer planning RRSO, identified by treating clinicians in gynaecology-oncology and familial cancer centers. The comparison group were a self-referring, community-based sample of similar-aged premenopausal women not planning oophorectomy or pregnancy in the next 2 years. Premenopausal status was confirmed by regular menstrual cycles, days 2 to 6 Follicle Stimulating Hormone (FSH) ≤15 IU/L and estradiol >100 pmol/L [14]. Exclusions for both groups included pregnancy or lactation in the past 3 months, unscheduled vaginal bleeding or use of anti-estrogens [15]. Participants were recruited from 5 sites, 4 in Australia and 1 in the USA. All participants provided written informed consent as previously described [15]. Baseline data were collected within 8 weeks of eligibility screening, and RRSO was scheduled between the baseline and 3 month study time-points [15].

2.2. Study assessments

Demographic data, medical, surgical, and gynaecological history, HT and hormonal contraceptive use were documented, and questionnaires were completed at the baseline, 3, 6 and 12 month study time-points. Dates of administration, type and dose of systemic HT were self-reported at each study time-point. All participants completed the Menopause-Specific Quality of Life Intervention Version (MENQOL-I) questionnaire [16]. The MENQOL-I captures 32 symptoms in four domains: vasomotor (3 items – hot flashes/flushes, night sweats and sweating), psychosocial (7 items), physical (19 items) and sexual (3 items) [16,17]. Participants indicated whether they experienced each symptom "in the past week" (no or yes) and rated the degree of symptom bother on a 7-point linear scale (from "not at all" to "extremely bothered"). Domain scores are calculated as the average of the item responses within each domain, with higher scores equating to greater bother. The total MENQOL-I score is the average of the four domain scores. The scale is validated and widely used [18,19]. Dichotomized responses (no/yes) to questions about hot flashes and night sweats were used to determine the prevalence of VMS. The degree of bother from VMS was determined from the MENQOL-I vasomotor domain score, whereby participants with scores between 2 and 5 were classified as having "mild" bother and those with scores between 6 and 8 as having "severe" bother [20].

2.3. Potential confounders

Potential confounders in the associations between RRSO and menopausal symptoms included age at baseline, previous clinician diagnosed anxiety or depression, body mass index (BMI) and smoking status at baseline and 12 months. BMI was classified using WHO criteria as underweight /normal (<25 kg/m^2), overweight (25 to <30 kg/m^2) or obese (≥30 kg/m^2). Smokers were categorized as non-smoker (never smoked), ex-smoker (ceased before baseline) or current smoker (smoker any time between baseline and 12 months).

2.4. Statistical analysis

Descriptive statistics were generated to check cell sizes in categorical variables and distribution shape and outliers in continuous variables. A small number of outliers were detected and winsorized (value reduced so they were no longer outliers but maintained their rank within the distribution). The differences in prevalence of VMS between the RRSO and comparison groups, and between HT users and non-users were examined using Chi-square tests. Multilevel models (proc mixed) were used to compare change over time, and differences at 12 months in RRSO and comparison groups and HT users and non-users. Time (months) centered at 12 months and continuous total MENQOL-I and individual domain scores were analyzed. The unadjusted multilevel models included time and either study group or HT use as the explanatory variables. The adjusted model was run twice, once with the baseline value of the outcome variable and all covariates, and again with only the covariates significant at $p < 0.10$ (less stringent statistical significance criteria due to smaller sample size). Models were repeated with the winsorized variables as a sensitivity analysis. Statistical significance was set at $p < 0.05$ and statistical analysis was conducted in SAS (version 9.4, SAS Institute, North Carolina).

3. Results

3.1. Participant demographics

Of the 687 women screened between 2013 and 2019, $n = 224$ met inclusion criteria and were willing to participate and 194 women were included in this analysis (RRSO group: $n = 94$; comparison group: $n = 99$) (Fig. 1). Between the Baseline and 12 month study visits 30 of the 224 eligible participants were withdrawn from the study. This included: (i) 18 who did not meet the inclusion criteria for Baseline estradiol and/or FSH levels, (ii) 8 who revoked consent – prior to the 3 month ($n = 2$), 6 month (n = 2) and 12 month ($n = 4$) study visits, (iii) 3 who were lost to follow-up – prior to the 6 month (n = 2) and 12 month ($n = 1$) study visits, and (iv) 1 who completed the two-year study but did not attend the 3, 6 and 12 month study visits (Fig. 1). Mean ages at baseline of the two groups were very similar

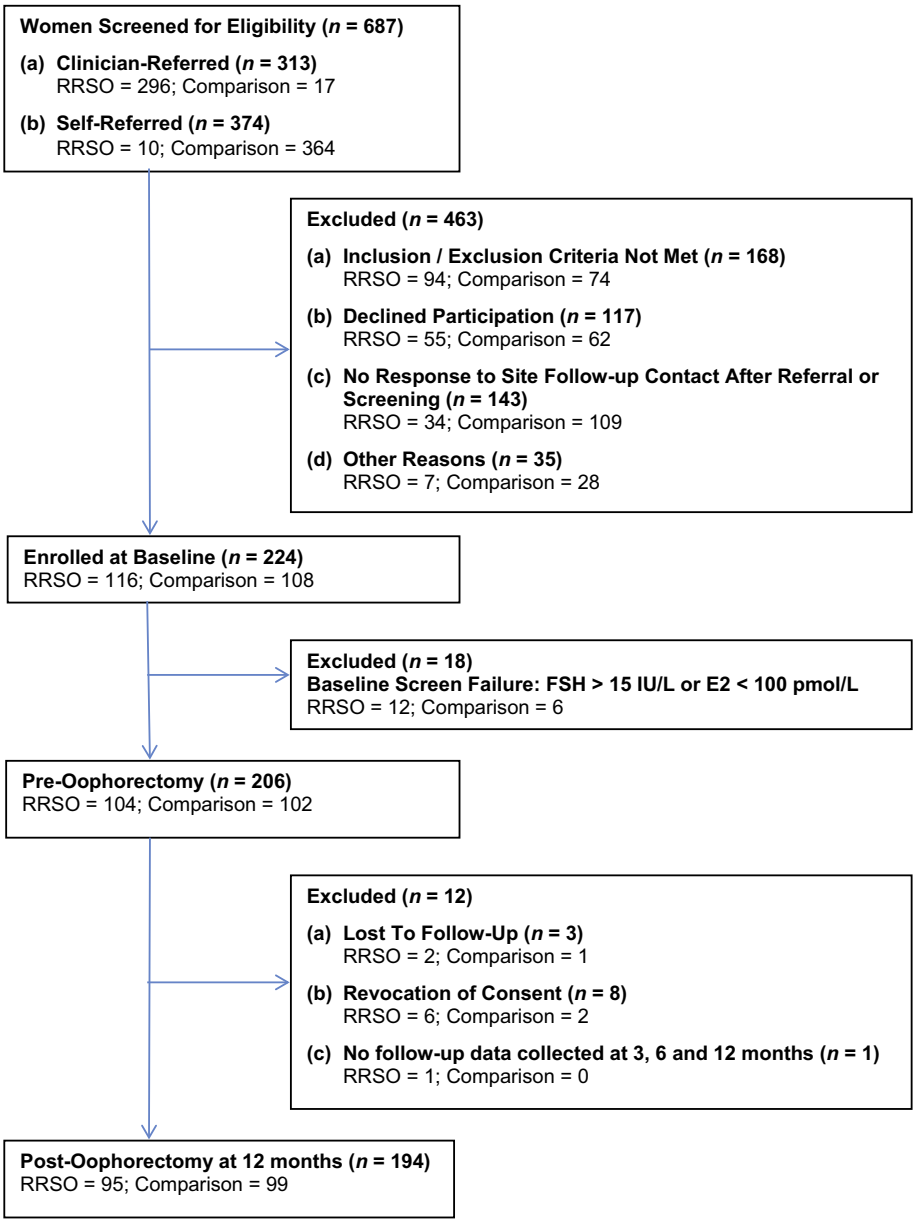

Fig. 1. Participant Flowchart. Number of participant screenings, enrolments, withdrawals and exclusions relevant to the first 12 months of the WHAM study. Women were either clinician- or self-referred to one of five recruitment sites in Australia and the USA during 2013 to 2019. *FSH* = Follicle-Stimulating Hormone; *E2* = Estradiol.

(RRSO 41.5 +/− SD 5.1 years vs comparisons 40.8 +/-SD 5.8, $p = 0.074$) (Table 1). BMI and smoking status did not differ between groups but more RRSO participants were overweight/obese (61% versus 46.5%; $p = 0.078$) (Table 1). More participants in the RRSO group had a history of breast cancer (11.6% vs 2%, $p = 0.008$) and one developed breast cancer during the study. Thirty-one percent of the RRSO group had concurrent hysterectomy with RRSO (Table 1). No occult ovarian cancers were detected but one case of serous tubal intraepithelial carcinoma was identified. None of the comparison group underwent oophorectomy during the study period.

3.2. Use of systemic hormone therapy (HT)

No participants were using HT at baseline. After RRSO, 60% (57/95) initiated HT, most (47/57, 82.5%) within 3 months of RRSO and all continued for 12 months. Only 10 (17.5%) delayed initiation of HT beyond 3 months after RRSO. Of those who did intiate HT within 3 months, 66% (31/47) started HT within the first week after surgery. The estrogen dose in HT was clinically determined. Of the 57 HT users, 23 (40.4%) used oral estrogen formulations, 31 (54.4%) used transdermal estrogen formulations and 3 (5.2%) used tibolone. Of those taking estrogen-containing HT, most (45/57, 78.9%) took doses equivalent to 50 μg/day or greater of transdermal estradiol or 1 mg/day or greater of oral estradiol. Only three participants (5.3%) took <50 μg/day. Over the study period eight (14%) varied their HT dose - 7 increased the estrogen dose and 1 decreased the dose. In one participant the HT dose was unknown. Only 4 participants used vaginal estrogen after RRSO - two in addition to systemic HT and two used vaginal estrogen alone.

3.3. Vasomotor symptoms (VMS)

The prevalence of VMS increased between baseline and 3 months after RRSO ($p < 0.001$) and was significantly higher than the comparison group at 3, 6 and 12 months (all $p < 0.001$) (Fig. 2). The overall

Table 1
Demographic characteristics of overall sample and by study group.

Characteristic (n, %)		By Study Group		
	Overall $n = 194$	Comparison $n = 99$	RRSO $n = 95$	p[a]
Age (years) at baseline (mean, SD)	41.5 (5.1)	40.8 (5.8)	42.1 (4.2)	0.074
BMI (kg/m^2) at baseline				
< 25 (Under/Normal)	90 (46.4)	53 (53.5)	37 (39.0)	0.078
25 to <30 (Overweight)	60 (30.9)	29 (29.3)	31 (32.6)	
≥ 30 (Obese)	44 (22.7)	17 (17.2)	27 (28.4)	
Hysterectomy[b]				
No	159 (82.0)	95 (96.0)	64 (67.4)	<0.001
Yes	35 (18.0)	4 (4.0)	31 (32.6)	
Previous breast cancer at baseline[c]				
No	181 (93.3)	97 (98.0)	84 (88.4)	0.008
Yes	13 (6.7)	2 (2.0)	11 (11.6)	
Pathogenic genetic variants[d]				
BRCA				
No/unknown	117 (60.3)	94 (95.0)	23 (24.2)	–
BRCA1	38 (19.6)	2 (2.0)	36 (37.9)	
BRCA2	35 (18.0)	3 (3.0)	32 (33.7)	
BRCA1 & 2	4 (2.1)	0 (0)	4 (4.2)	
Lynch syndrome (*MLH1, MSH6, PMS2*)				
No/unknown	189 (97.4)	98 (99.0)	91 (95.8)	–
Yes	5 (2.6)	1 (1.0)	4 (4.2)	
Other pathogenic variants (*STK11, BRIP1*)				
No/unknown	192 (99.0)	99 (100)	93 (97.9)	–
Yes	2 (1.0)	0 (0)	2 (2.1)	
Hormonal contraception at baseline				
No	115 (59.3)	53 (53.5)	62 (65.3)	0.097
Yes	79 (40.7)	46 (46.5)	33 (34.7)	
Smoking status				
Non-smoker	117 (60.3)	60 (60.6)	57 (60.0)	0.719
Ex-smoker	62 (32.0)	30 (30.3)	32 (33.7)	
Smoked during WHAM	15 (7.7)	9 (9.1)	6 (6.3)	

[a] Chi-square test not performed where cell sizes were too small.
[b] One RRSO and three comparison participants had hysterectomy prior to Baseline. One comparison participant underwent hysterectomy (ovaries retained) during the follow-up period.
[c] One RRSO participant developed breast cancer over the follow-up period.
[d] Pathogenic genetic variants known to increase ovarian cancer risk.

prevalence of VMS was 55% which remained stable between 3 and 12 months (Fig. 2). Multilevel regression models, readjusted for baseline values, age and BMI at baseline, previous depression or anxiety, and smoking status showed that VMS severity (as measured by bother) had increased by 3 months after RRSO and remained elevated at 12 months (Fig. 3 and Tables S1 and S2). In participants with VMS at 3 months ($n = 58$), VMS bother was categorized as "mild" in 86% and as "moderate" or "severe" in only 14% (Table S3). This pattern of VMS bother did not significantly change over the 12-month follow-up period (Table S3).

3.4. Menopause-related quality of life (QoL)

Overall menopause-related QoL worsened between baseline and 3 months in the RRSO group but not in the comparison group (Tables S1 and S2). The MENQOL-I subscale scores indicated that worsening QoL after RRSO was driven by an increase in vasomotor, sexual, and physical symptom domains. There were no differences between groups in the psychosocial domain of the MENQOL-I (Tables S1 and S2). Results did not differ when analyses were conducted using the winsorized variables as a sensitivity analysis (data not shown).

3.5. Effects of hormone therapy (HT)

After RRSO, VMS were less common in HT users (60%) compared to non-HT users (40%). However, VMS persisted despite HT use. At 3 months, 39.6% of HT users reported hot flashes versus 80.6% of non-HT users and this pattern persisted over 12 months (Fig. 4). At 3 months, there was little difference between HT users and non-HT users in the prevalence of night sweats (41.5% in HT users versus 55.6% in non-HT users), but by 6 months the prevalence of night sweats was halved in HT users compared to non-HT users (35.1% vs 68.6%) (Fig. 4). Multilevel models indicated that HT significantly reduced VMS bother at all time-points (Fig. 5 and Table S4). In non-HT users, VMS bother remained constant over the 12-month follow-up period (Fig. 5). Adjusted multilevel regression models showed that HT improved overall QoL and sexual function compared to non-HT users (Table S4). However, use of HT did not restore overall menopause-related QoL or sexual function to baseline levels (Table S5). Use of HT did not affect the physical or psychosocial domains of the MENQOL-I.

4. Discussion

This is the largest prospective studies of VMS after premenopausal RRSO to include a premenopausal control group. Following RRSO, we observed a substantial increase in the prevalence of VMS, which were reported by around 40% of HT users and 80% of non-HT users by 3 months. These persisted and did not return to baseline levels by 12 months. However, the overall prevalence of VMS (50%), including those who did and did not take HT, was somewhat less than that reported in population-based studies of the natural menopause transition (75 to 85%) [21]. We observed that VMS were not inevitable after premenopausal RRSO. Of the non-HT users around 20% reported no hot flashes and 45% no night sweats over 12-months.

Vasomotor symptoms are thought to be more severe following premenopausal oophorectomy compared to natural menopause [22]. However, almost all WHAM RRSO participants described the severity of VMS (as measured by bother) as "mild" (86%) and only 14% classified their VMS as "moderate" or "severe", and this included HT users and

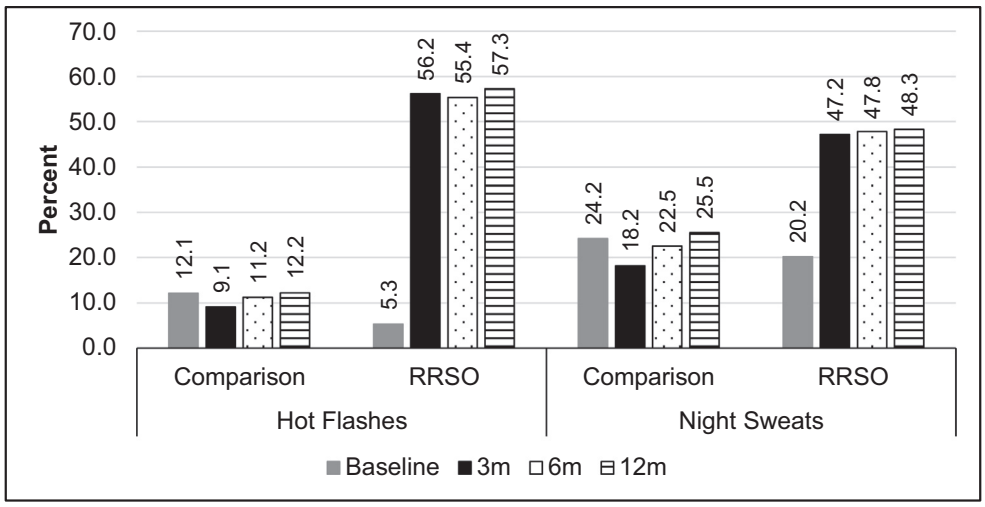

Fig. 2. Prevalence (%) of hot flashes and night sweats from baseline to 12 months in the RRSO and comparison groups.
Note. Prevalence of vasomotor symptoms was determined by answers of "no" or "yes" on the hot flashes and night sweats questions of the intervention version of the Menopause-Specific Quality of Life (MENQOL-I) questionnaire.

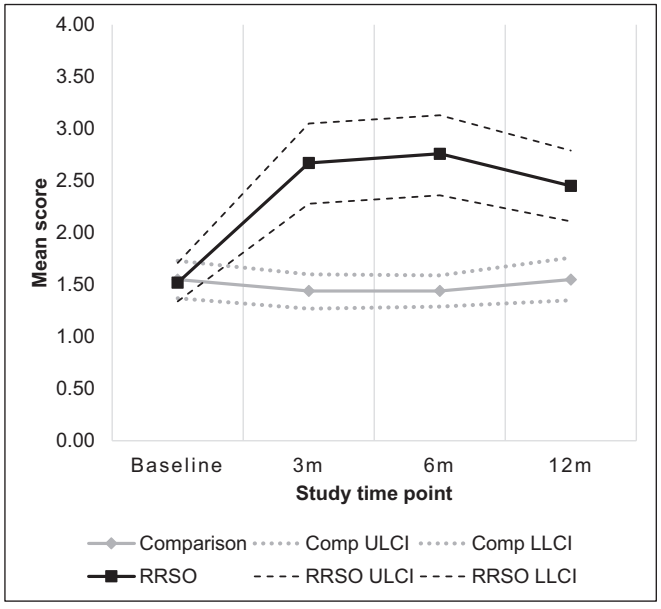

Fig. 3. Degree of bother (mean, 95% confidence interval) from vasomotor symptoms in RRSO and comparison groups.
Note. Bother is measured by the vasomotor domain of the intervention version of the Menopause-Specific Quality of Life (MENQOL-I) questionnaire. *ULCI: Upper limit for the 95% confidence interval; LLCI: Lower limit for the 95% confidence interval.*

non-HT users. Whilst we did not have a control group transitioning natural menopause to compare VMS severity, population-based studies of natural menopause using the same severity measure report that around one quarter experience "moderate to severe" VMS [23,24]. Women considering RRSO are very concerned about the prospect of severe VMS [13]. Together, our findings suggest that bothersome VMS are not inevitable after premenopausal RRSO and may not be worse than those experienced over the natural menopause transition. However, RRSO led to a decline in overall, QoL in vasomotor, sexual and physical domains of the MENQOL-I. Thus more information is needed about the severity and duration of VMS and effects on quality of life following RRSO compared to those experienced transitioning natural menopause.

Following RRSO the uptake of HT was around 60% which is similar to previous publications [25]. Use of HT was not randomized in this study and it is likely that women with more troublesome VMS were more likely to take HT. Consistent with previously published studies, we found that HT reduced but did not fully resolve VMS after RRSO [9,26,27]. At three months, around 40% of HT users continued to report hot flashes and HT had little impact on the prevalence of night sweats. Compared to baseline, this represented an 8-fold increase in the prevalence of hot flashes at three months despite HT use. Over the natural menopause transition HT reduces VMS by around 85% [11]. Together, these data suggest that HT may be less effective for VMS after RRSO compared to natural menopause, at least during the initial months. By 6–12 months HT effectively reduced both the prevalence and severity of VMS. In non-HT users (40%) the severity of VMS was consistent between 3 and 12 months. In WHAM the dose of estrogen in HT was not standardized but most RRSO participants (66.7%) were taking estradiol doses of 50–75 μg/day (data not shown). The optimal dose and duration of estrogen following early menopause is uncertain [28]. In women with spontaneous premature ovarian insufficiency the general population higher doses of estrogen (up to 100 μg/day) are recommended [29]. In this study it is possible that higher doses of estrogen may have been more effective for VMS. However, we found no association between estrogen dose and prevalence or VMS bother (data not shown). In addition, the safety of high dose estrogen (and progestin) in women at elevated risk of breast cancer is uncertain. Women considering HT after RRSO should be aware that it may not fully resolve their VMS, particularly night sweats.

Menopause-related QoL was reduced after RRSO reflecting changes in vasomotor, physical and sexual domains. Our findings differ from previous studies demonstrating that RRSO does not lead to worse QoL compared with ovarian cancer screening [25]. However, this study included many women who were already peri- or post-menopausal at baseline and may not reflect the true impact of premenopausal oophorectomy on QoL. Similar to the effects on VMS, use of HT did not restore sexual or physical domains of the MENQOL-I to baseline levels. Women considering RRSO should be aware of the potential for persistent adverse effects on QoL, particularly sexual and physical symptoms, and that HT may mitigate but not restore symptoms to pre-operative levels. More information is needed about the optimal type, dose and duration of HT in this population.

The MENQOL-I includes psychological symptoms which did not change following RRSO or with HT use. Our findings suggest that psychological symptoms such as "dissatisfaction with my personal life" and "feelings of wanting to be alone" are not menopausal symptoms.

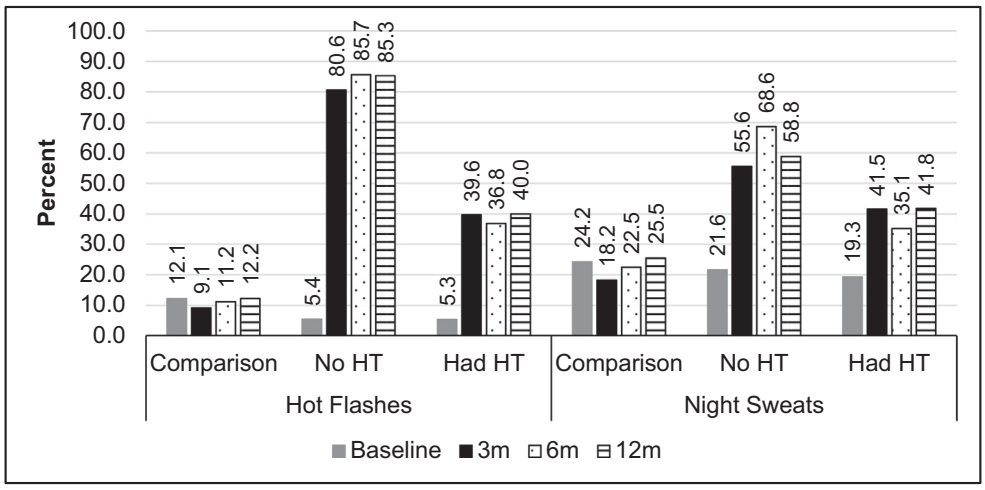

Fig. 4. Prevalence (%) of hot flashes and night sweats from baseline to 12 months by HT use in RRSO participants.
Note. Prevalence of vasomotor symptoms was determined by answers of "no" or "yes" on the hot flashes and night sweats questions of the intervention version of the Menopause-Specific Quality of Life (MENQOL-I) questionnaire.

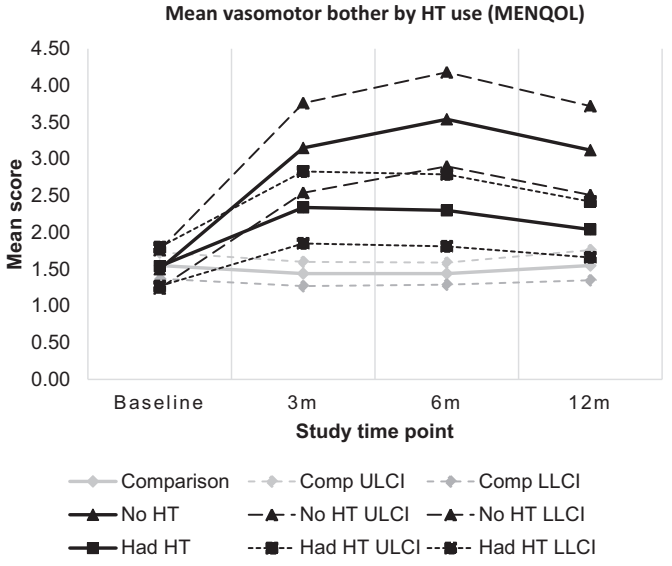

Fig. 5. Degree of bother (mean, 95% confidence interval) from vasomotor symptoms by HT use in RRSO participants.
Note. Bother is measured by the vasomotor domain of the intervention version of the Menopause-Specific Quality of Life (MENQOL-I) questionnaire. *ULCI: Upper limit for the 95% confidence interval; LLCI: Lower limit for the 95% confidence interval.*

Including these symptoms in menopause scales may artificially inflate the apparent symptom burden of menopause with potential negative consequences for women [30].

Strengths of the WHAM study include the relatively large sample size, inclusion of a premenopausal comparison group of a similar age who retained their ovaries, use of validated measures and the prospective study design. Limitations include use of hormonal contraception at baseline, but this was not associated with vasomotor or QoL outcomes after RRSO. Vasomotor symptoms were not measured until 3 months which may have missed more severe symptoms immediately after RRSO. We did not measure cancer worry and this may have affected quality of life. The study was not randomized and women with more severe VMS may have been more likely to use HT. Also, the estrogen dose in HT was not standardized and may have been too low for the effective management of VMS. Obesity has been associated with more frequent VMS [31]. More women in the RRSO group were obese (28%) compared to the comparison group (17%) which may have affected our findings. Most participants were white and our findings may not be generalizable to other races [32].

Women considering RRSO want to know what symptoms to expect and how best to manage them [13]. Our findings suggest that VMS increase and QoL worsens for some women after RRSO, and that HT improves these symptoms but not to pre-oophorectomy levels. However, in most cases (86%) bother due to VMS was categorized as "mild" suggesting that severe VMS are not inevitable in this population. There is an unmet need for consensus guidance on managing women following RRSO [33–35]. These findings will inform evidence-based clinical guidance for this population.

Declaration of Competing Interest

MH is an editor for the Cochrane Gynaecology and Fertility Group Editorial Board and has received pharmaceutical funding from QUE Oncology P/L, Madorra P/L and Ovoca Bio (Australia) P/L for clinical research outside of the submitted work. *CDW has received sponsorship and honoraria from Biogen and Seqirus and is the Deputy Chair (Honorary) of VCS Foundation P/L.* SMD has received personal fees from AstraZeneca outside of the submitted work. KMM, EOK, AB, JK, HLS, TT-B, AT and GDM have no competing interests to declare.

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GDM is supported by a NHMRC Principal Research Fellowship (ID # APP1121844).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.07.029.

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